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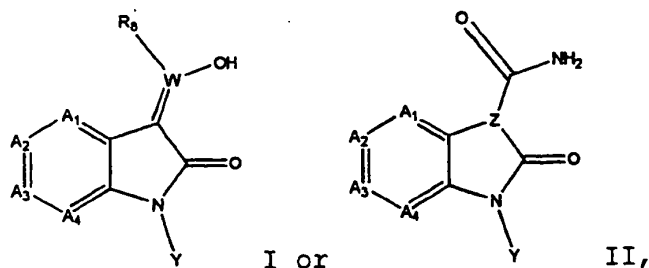
<p>(51) International Patent Classification <sup>7</sup> : C07D 209/40, A61K 31/395, A61P 43/00, C07D 413/06, 405/06, 417/06, 401/06, 403/06, 409/04, 409/14, 405/14, 417/14, 401/14, C07F 7/10</p>	<p>A1</p>	<p>(11) International Publication Number: <b>WO 00/64872</b>  (43) International Publication Date: 2 November 2000 (02.11.00)</p>
<p>(21) International Application Number: PCT/US00/10866  (22) International Filing Date: 21 April 2000 (21.04.00)  (30) Priority Data: 60/130,752 23 April 1999 (23.04.99) US  (71) Applicant (for all designated States except US): VERTEX PHARMACEUTICALS INCORPORATED [US/US]; 130 Waverly Street, Cambridge, MA 02139-4242 (US).  (72) Inventors; and (75) Inventors/Applicants (for US only): SALITURO, Francesco, Gerald [US/US]; 25 Baker Drive, Marlborough, MA 01752 (US). BEMIS, Guy, W. [US/US]; 256 Appleton Street, Ar- lington, MA 02476 (US). WILKE, Susanne [DE/US]; 16 Rindgefield Street, Cambridge, MA 02140 (US). GREEN, Jeremy [US/US]; 21 Greystone, Burlington, MA 01803 (US). CAO, Jingrong [CN/US]; 45 Madison Avenue, New- ton, MA 02460 (US). GAO, Huai [CN/US]; 26 Lane's End, Natick, MA 01760 (US). HARRINGTON, Edmund, Martin [IE/US]; Apartment #21, 284 Harvard Street, Cambridge, MA 02139 (US).</p>	<p>(74) Agents: HALEY, James, F., Jr.; Fish &amp; Neave, 1251 Avenue of the Americas, New York, NY 10020 (US) et al.  (81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: INHIBITORS OF c-JUN N-TERMINAL KINASES (JNK)</p> <p>(57) Abstract</p> <p>The present invention relates to compounds of formula (I) or (II), or a pharmaceutically acceptable derivative or prodrug thereof; wherein Y is selected from <math>-(CH_2)-Q_1</math>; <math>-(CO)-Q_1</math>; <math>-(CO)NH-Q_1</math>; <math>-(CO)-O-Q_1</math>; <math>-(SO_2)-Q_1</math> or <math>-(SO_2)NH-Q_1</math>; <math>Q_1</math> is a <math>C_1-C_6</math> straight chain or branched alkyl or alkenyl group; a 5-7 membered aromatic or non-aromatic carbocyclic or heterocyclic ring; or a 9-14 membered bicyclic or tricyclic aromatic or non-aromatic carbocyclic or heterocyclic ring system, W is N or C; Z is CH or N, which are inhibitors of JNK, a mammalian protein kinase involved cell proliferation, cell death and response to extracellular stimuli. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders.</p>		

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CLAIMS

We claim:

1. A compound of the formula:



or a pharmaceutically acceptable derivative or prodrug thereof; wherein

Y is selected from  $-(CH_2)-Q_1$ ;  $-(CO)-Q_1$ ;  $-(CO)NH-Q_1$ ;  $-(CO)-O-Q_1$ ;  $-(SO_2)-Q_1$  or  $-(SO_2)NH-Q_1$ ;

$Q_1$  is a  $C_1-C_6$  straight chain or branched alkyl or alkenyl group; a 5-7 membered aromatic or non-aromatic carbocyclic or heterocyclic ring; or a 9-14 membered bicyclic or tricyclic aromatic or non-aromatic carbocyclic or heterocyclic ring system, wherein said alkyl, alkenyl, ring or ring system is optionally substituted with one to four substituents, each of which is independently selected from  $NH_2$ ,  $NH-R$ ,  $N(R)_2$ ,  $NO_2$ ,  $OH$ ,  $OR$ ,  $CF_3$ , halo,  $CN$ ,  $CO_2H$ ,  $C(O)-NH_2$ ,  $C(O)-NH-R$ ,  $C(O)-N(R)_2$ ,  $C(O)-R$ ,  $SR$ ,  $S(O)-R$ ,  $S(O)_2-R$ ,  $S(O)_2-NH-R$  or  $-R$ ;

W is N or C;

wherein when W is N,  $R_8$  is a lone pair of electrons; and

wherein when W is C,  $R_8$  is  $R_7$ .

$A_1$  is N or  $CR^1$ ;

$A_2$  is N or  $CR^2$ ;

$A_3$  is N or  $CR^3$ ;

$A_4$  is N or  $CR^4$ ;

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provided that at least one of  $A_1$ ,  $A_2$ ,  $A_3$  and  $A_4$  must not be N;

$R^1$  is  $-NHR^5$ ,  $-OR^5$ ,  $-SR^5$ , or  $-R^5$ ;

$R^2$ ,  $R^3$ , and  $R^4$  are independently selected from -  
5 (CO)NH<sub>2</sub>, -(CO)NHR, -(CO)N(R)<sub>2</sub>, -NHR<sup>5</sup>, -NHCH<sub>2</sub>R<sup>5</sup>, -OR<sup>5</sup>, -SR<sup>5</sup>, -  
R<sup>5</sup>, -NH(CO)-R<sup>6</sup>, -NH(CO)-NHR<sup>6</sup>, -NH(CO)-NH(CO)R<sup>6</sup>, -NH(CO)-OR<sup>6</sup>,  
-NH(SO<sub>2</sub>)-R<sup>6</sup>, -NH(SO<sub>2</sub>)-NHR<sup>6</sup>, -C(O)OH, -C(O)OR, -(CO)-Q<sub>1</sub>, -  
(CO)NH-Q<sub>1</sub>, -(CO)NR-Q<sub>1</sub>, -(CO)-O-Q<sub>1</sub>, -(SO<sub>2</sub>)-Q<sub>1</sub> or -(SO<sub>2</sub>)NH-Q<sub>1</sub>;

$R^5$  and  $R^6$  are each independently selected from H;  
10 N(R)<sub>2</sub>, NHOH, NO<sub>2</sub>, C(O)OR or halo; a C<sub>1</sub>-C<sub>6</sub> straight chain or  
branched alkyl, alkenyl or alkynyl group; a 5-7 membered  
aromatic or non-aromatic carbocyclic or heterocyclic ring;  
or a 9-14 membered bicyclic or tricyclic aromatic or non-  
aromatic carbocyclic or heterocyclic ring; wherein said  
15 alkyl, alkenyl, ring or ring system is optionally  
substituted with one to four substituents, each of which  
is independently selected from NH<sub>2</sub>, NHR, NHC(O)OR, N(R)<sub>2</sub>,  
NO<sub>2</sub>, OH, OR, CF<sub>3</sub>, halo, CN, Si(R)<sub>3</sub>, CO<sub>2</sub>H, COOR, CONH<sub>2</sub>,  
CONHR, CON(R)<sub>2</sub>, COR, SR, S(O)R, S(O)<sub>2</sub>R, S(O)<sub>2</sub>NHR or R;

20  $R^7$  is H; a C<sub>1</sub>-C<sub>6</sub> straight chain or branched alkyl  
or alkenyl group; a 5-7 membered aromatic or non-aromatic  
carbocyclic or heterocyclic ring; or a 9-14 membered  
bicyclic or tricyclic aromatic or non-aromatic carbocyclic  
or heterocyclic ring; wherein said alkyl, alkenyl, ring or  
25 ring system is optionally substituted with one to four  
substituents, each of which is independently selected from  
NH<sub>2</sub>, NHR, N(R)<sub>2</sub>, NO<sub>2</sub>, OH, OR, CF<sub>3</sub>, halo, CN, CO<sub>2</sub>H, CONH<sub>2</sub>,  
CONHR, CON(R)<sub>2</sub>, COR, SR, S(O)R, S(O)<sub>2</sub>R, S(O)<sub>2</sub>NHR or R;

R is a C<sub>1</sub>-C<sub>6</sub> straight chain or branched alkyl or  
30 alkenyl group, a 5-7 membered aromatic or non-aromatic  
carbocyclic or heterocyclic ring, or a 9-10 membered  
bicyclic aromatic or non-aromatic carbocyclic or

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heterocyclic ring system; and

Z is CH or N.

2. The compound according to claim 1, wherein  
5 Y is  $-(CH_2)-Q_1$  and  $Q_1$  is a substituted phenyl.

3. The compound according to claim 1, wherein  
the compound is selected from any one of the compounds  
depicted in Table 1.

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4. A pharmaceutical composition comprising an  
amount of a compound according to any one of claims 1 to 3  
effective to inhibit JNK, and a pharmaceutically  
acceptable carrier.

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5. Use of the composition according to claim 4  
for the manufacture of a medicament for treating or  
preventing inflammatory diseases, autoimmune diseases,  
destructive bone disorders, proliferative disorders,  
20 infectious diseases, neurodegenerative diseases,  
allergies, reperfusion/ischemia in stroke, heart attacks,  
angiogenic disorders, organ hypoxia, vascular hyperplasia,  
cardiac hypertrophy, thrombin-induced platelet aggregation  
or conditions associated with proinflammatory cytokines in  
25 a patient in need thereof.

6. The use according to claim 5, wherein said  
treating or preventing is for an inflammatory disease  
selected from acute pancreatitis, chronic pancreatitis,  
30 asthma, allergies, or adult respiratory distress syndrome.

7. The use according to claim 5, wherein said

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treating or preventing is for an autoimmune disease selected from glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, or graft vs. host disease.

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8. The use according to claim 5, wherein said wherein said treating or preventing is for a destructive bone disorders selected from osteoarthritis, osteoporosis or multiple myeloma-related bone disorder.

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9. The use according to claim 5, wherein said wherein said treating or preventing is for a proliferative disease selected from acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, or multiple myeloma.

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10. The use according to claim 5, wherein said wherein said treating or preventing is for a neurodegenerative disease selected from Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia or neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity or hypoxia.

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11. The use according to claim 5, wherein said wherein said treating or preventing is for ischemia/reperfusion in stroke or myocardial ischemia,

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renal ischemia, heart attacks, organ hypoxia or thrombin-induced platelet aggregation.

12. The use according to claim 5, wherein said  
5 wherein said treating or preventing is for a condition associated with T-cell activation or pathologic immune responses.

13. The use according to claim 5, wherein said  
10 wherein said treating or preventing is for an angiogenic disorder selected from solid tumors, ocular neovascularization, or infantile haemangiomas.

In. .ational Application No  
PCT/US 00/10866

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# INTERNATIONAL SEARCH REPORT

In. .ational Application No  
PCT/US 00/10866

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	<p>CHEMICAL ABSTRACTS, vol. 90, no. 19, 7 May 1979 (1979-05-07) Columbus, Ohio, US; abstract no. 152060r, ABRAMENKO, P. I. ET AL.: "Synthesis of substituted indolothiazoles and thienothiazoles." XP002147703 abstract &amp; ZH. VSES. KHIM. O-VA., vol. 23, no. 6, - 1978 pages 711-712, -&amp; DATABASE CHEMICAL ABSTRACTS 'Online! CA 90:152060, XP002147710 compound with RN 69736-62-5 and -61-4</p>	1
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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/10866

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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